## REMARKS

This Amendment, filed in reply to the Office Action dated July 22, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 5, 6 and 27-46 are rejected. Claim 5 is amended herewith to incorporate the subject matter of Claims 44 and 46 therein. Claim 7 is amended herewith solely to improve clarity. Claims 42-46 are canceled herewith without prejudice or disclaimer.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

### Withdrawn Rejections

**1.** Applicants thank the Examiner for withdrawing the rejection of Claims 34, 37, 38, 40 and 41 under 35 U.S.C. § 112, first paragraph.

**2.** Applicants thank the Examiner for withdrawing the rejection of Claims 5, 6 and 27-46 under 35 U.S.C. § 102(b) as allegedly being anticipated by Shitara *et al.*

### Claims 5, 6 and 27-46 are Patentable Under 35 U.S.C. § 103

On page 3 of the Office Action, Claims 5, 6 and 27-46 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Shitara *et al.* (U.S. Patent Publication No. 2003/0175273, of record) in view of Taub *et al.* (U.S. Patent No. 6,762,174).

In making the rejection, the Examiner contends that Shitara *et al.* discloses a method for treating CCR4-related cancer, more particularly leukemia and lymphoma, comprising administering an anti-CCR4 antibody possessing ADCC activity. However, the Examiner

asserts that Shitara *et al.* does not specifically teach administration of the anti-CCR4 antibody in an *unconjugated* form, and administration of at least one agent, as claimed. Nevertheless, the Examiner alleges that Shitara *et al.* discloses that the antibody can be administered as the active ingredient in a pharmaceutical formulation, and that Shitara *et al.* discloses that the antibody exhibits ADCC activity, such that one of ordinary skill in the art would have understood that the *unconjugated* antibody would exhibit therapeutic activity *by itself*, through ADCC of CCR4-expressing cancer cells.

The Examiner further contends that one of ordinary skill in the art would readily have combined such an unconjugated anti-CCR4 antibody with an additional therapeutic agent, such as vincristine, cyclophosphamide, etoposide or methotrexate. Motivation for such a combination is alleged to be found in Taub *et al.*, who allegedly discloses a combination therapy containing a compound encompassed by Formula I therein and an anti-cancer agent such as vincristine, cyclophosphamide, etoposide or methotrexate. In view of the alleged synergy exhibited by the combination therapy of Taub *et al.*, the Examiner takes the position that one of ordinary skill in the art would readily have combined a therapeutic agent, such as vincristine, cyclophosphamide, etoposide or methotrexate, with the antibody composition of Shitara *et al.* "for the advantage of synergism (*e.g.*, decreasing dose-limiting side effects)." Similarly, the Examiner contends that one of ordinary skill in the art would readily have combined a cytokine, such as G-CSF, M-CSF or IL-2, with the antibody composition of Shitara *et al.*, so as to activate immune cells, thereby boosting the patient's immune response against the cancer, citing paragraph [0163] of Shitara *et al.* in support.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

It is well-settled that a showing of an unexpected property or result, or a greater than expected result, may be sufficient to rebut a finding of obviousness. Relevant law holds that such an unexpected result may be demonstrated by, for example, a comparison vis-à-vis the closest prior art, demonstrating unpredictability in the pertinent art area such that one of ordinary skill in the art would not expect the claimed product to possess the properties it does (See *In re May*, 197 USPQ 601 (C.C.P.A. 1978)), or demonstrating an effect greater than the sum of each of the effects taken separately (*i.e.*, a demonstration of synergy). See *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989).

As discussed below, Applicants demonstrate that the claimed method, *i.e.*, the treatment of a CCR4-expressing tumor in a patient, comprising administering to the patient a recombinant antibody or antigen-binding fragment thereof that specifically binds to human CC chemokine receptor 4 (CCR4), and at least one agent selected from the group consisting of G-CSF, M-CSF, interferon-α, IL-2, IL-15, vincristine, cyclophosphamide, etoposide and methotrexate, which is not conjugated to the antibody or antigen-binding fragment, exhibits synergy with regard to the treatment of CCR4-expressing tumors *in vivo,* and that such synergy would have been unexpected to those of ordinary skill in the art.

Specifically, Applicants respectfully refer the Examiner to the data depicted in Figures 1-7, and Table 7, of the Application as filed, which demonstrate the unexpected superior efficacy of the combination of anti-CCR4 antibody/IL-2 (Figure 1; Example 1), anti-CCR4 antibody/IL-15 (Figure 1; Example 1), anti-CCR4 antibody/vincristine (Figure 2; Example 2), anti-CCR4 antibody/cyclophosphamide (Figure 3; Example 3), anti-CCR4 antibody/etoposide (Figure 4; Example 4), anti-CCR4 antibody/methotrexate (Figure 5; Example 5), anti-CCR4 antibody/G-CSF (Figure 6; Example 6), anti-CCR4 antibody/interferon-α (Figure 7; Example 7), and anti-

CCR4 antibody/M-CSF (Table 7; Example 8). Moreover, throughout the specification, such as at, for example, the paragraph bridging pages 37 and 38, the paragraph bridging pages 39 and 40, the paragraph bridging pages 41 and 42, page 44, first full paragraph, the paragraph bridging pages 46 and 47, page 49, fourth full paragraph, and the paragraph bridging pages 51 and 52, Applicants experimentally confirm that the efficacy of administration of the anti-CCR4 antibody and the claimed agents, unconjugated, is greater than the sum of each of the effects taken separately, and thus is synergistic.

Applicants submit that such synergy could not have been predicted, much less expected, by one of ordinary skill in the art, and is thus probative of the non-obviousness of the presently claimed invention, and at least because of the considerable unpredictability in the art as to which combinations of anti-cancer therapies exhibit synergy with an antibody against a particular antigen; indeed, such unpredictability is evident in the specification as filed. For example, as discussed on pages 2-4 of the specification as filed, while the state of the art at the time of the invention recognized that some combination therapies containing therapeutic antibodies, such as retuximab in combination with multiple drugs, could show synergy, the art also recognized that other combinations with the same antibody, such as retuximab in combination with IL-2 or GM-CSF, did not. Because of such unpredictability, and because the state of the art at the time of the invention did not even suggest synergy in the treatment of CCR4-expressing tumors with anti-CCR4 antibodies and the presently claimed agents, one of ordinary skill in the art could not have predicted or expected the presently claimed method to possess the beneficial properties it does. See *In re May*, 197 USPQ 601 (C.C.P.A. 1978). Indeed, while the rejection is premised on the basis that one of ordinary skill in the art would have combined the anti-CCR4 antibody composition of Shitara *et al.* with another anti-cancer treatment (without conjugation) "for the

advantage of synergism," Applicants note that the synergy referred to by Taub *et al.* is made in the narrow context of combination therapies *containing compounds encompassed by formula 1* therein, not antibodies. Taub *et al.* neither suggests, nor incites any expectation, that *any* given combination of anti-cancer therapies would exhibit synergy, much less that combination therapies specifically containing therapeutic antibodies would be *expected* to exhibit synergy. To the contrary, the synergy exhibited by anti-CCR4 antibodies (when used in combination with at least one agent recited in Claim 5), experimentally demonstrated by Applicants, would have been entirely *unexpected* to those of ordinary skill in the art, and thus non-obvious. In view of the state of the art at the time of the invention, the superior results of the claimed method are entirely unexpected, and their practical significance self-evident.

In view of the foregoing, Applicants respectfully submit that the claimed invention is not rendered obvious by the cited references.

Withdrawal of the rejection is respectfully requested.

**Double Patenting**

On page 6 of the Office Action, Claims 5, 6 and 27-46 are *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 54, 57-70, 74-75 and 81-84 of earlier-filed copending Application No. 11/969,555, in view of Shitara *et al.* (U.S. Patent Application Pregrant Publication No. 2003/0175273) and Taub *et al.* (U.S. Patent No. 6,762,174). Specifically, the Examiner contends that both Applications are directed to the treatment of CCR4-related blood cancer, comprising administering the same or nearly the same anti-CCR4 antibody.

Because this rejection is merely provisional in nature, Applicants respectfully request that it be held in abeyance until such time as allowable subject matter is identified.

**Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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